Image 1644 AF$

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
WALLER et al.	)	Art Unit: 1644
	)	
Application No. 09/945,339	)	Examiner: Belyavskyi, Michail A.
	)	
Filing Date: August 31, 2001	)	Confirmation No. 1418
	)	
For: METHODS OF TRANSPLANTATION USING CHEMOTHERAPY-TREATED ALLOGENEIC CELLS THAT ENHANCE IMMUNE RESPONSE WITHOUT GRAFT VERSUS HOST DISEASE	)	

APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

This is an appeal from the final rejection of claims 1-6 and 15-20 in the Office Action mailed April 9, 2003. A Notice of Appeal was mailed on October 9, 2003.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Emory University.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellants, the undersigned, or appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-58 are pending. Claims 7-14 and 21-58 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-6 and 15-20 stand rejected. Claims 1-6 and 15-20 are on appeal. The text of the claims on appeal are set forth in an appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

No amendments after final rejection have been filed.

(5) SUMMARY OF THE INVENTION

The present application solves a problem that has continually plagued transplants. That is, how to enhance transplant engraftment from matched unrelated or unmatched sibling donors without increasing the incidence of fatal graft versus host disease (GvHD). The removal of T cells from the bone marrow results in a decreased incidence of graft vs. host reactions, but an increased incidence of rejection of the allogeneic bone marrow graft by the patient. Thus, lymphocytes, and especially T cells, present in the allogeneic bone marrow graft are important to ensure engraftment in antigenically and genetically mis-matched recipients. The claims on appeal are drawn to methods of reducing GvHD in a transplant recipient by administering to the recipient in combination with hematopoietic cells, mononuclear cells which are treated so as to substantially reduce their ability to cause GvHD while they retain their ability to proliferate. In particular, the claims on appeal focus on three features (1) treating mononuclear cells to reduce their ability to cause GvHD (which is described at least on page 1, line 16; page 6, lines 6-7; page 6, line 21; page 15, lines 18-19, and page 18, lines 19-20), (2) the treated cells retain the ability to proliferate (which is described at least on page 1, lines 16-17; page 6, line 7; page 6, lines 21-22; page 15, line 19, and page 18, line 20), and (3) the treated cells are administered to the transplant recipient (which is described at least on page 6, lines 4-6; page 6, lines 19-20; and page 15, lines 16-18). The dependent claims 2-4 and 16-18 refer to the type of mononuclear cells which may be treated. Such types of mononuclear cell are described at least on page 9, lines 10-21; and page 17, line 1 through page 18 line 17. Dependent claims 5, 6, 19, and 20 refer to the type of treatment used on the mononuclear cells. Such treatments are described at least on

page 9, lines 10-21 page 18, line 19 through page 19, line 17; and page 27, line 14 through page 28, line 2, where chemotherapeutic agents are discussed and specific agents are described.

(6) ISSUES ON APPEAL

The issues presented on appeal are whether claims 1-6 and 15-20 are non-obvious as required by 35 U.S.C. § 103, over of Waller (US Patent 5,800,539) in view of Sykes et al (WO 99/25367).

(7) GROUPING OF CLAIMS

Claims 1-20 stand or fall together.

(8) ARGUMENTS

Claims 1-6 and 15-20 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,800,539 to Waller ("Waller") in view of Sykes et al. (WO 99/25367; "Sykes"). Appellants respectfully traverse this rejection.

1. The Issues

Appellants submit that the present rejection depends on the proper understanding of what the prior art discloses, the proper understanding of what the current claims require, the proper understanding of the law regarding 35 U.S.C. § 103(a) as it applies to the claimed methods, and a proper application of that law to the claimed methods. Appellants note that the Examiner has failed to achieve any of these goals in the present rejection.

The Examiner contends that the combination of Waller in view of Sykes renders the claimed invention obvious. In particular, the Examiner focuses on Sykes for its alleged disclosure of the ability of treated T cells to proliferate which is not disclosed in Waller. The Examiner states that motivation for the combination would be that "one of skill in the art at the time the invention was made would deduce from the combined reference teaching that a treatment of donor T cells in such a way as to retain not only their viability as taught by Waller, but also their ability to proliferate in the recipient, as taught by Sykes, would be essential to successful engraftment of donor hematopoeitic cells."

Appellants assert that (1) the combination of Waller and Sykes does not disclose or suggest the limitation of administering mononuclear cells treated so as to substantially reduce their ability cause graft versus host disease while they retain their ability to proliferate in the recipient, and (2) even if all the limitations were taught, the combination of Waller and Sykes is improper for the combination would change the principle of operation of Waller in that Waller discloses the nonproliferation of T cells.

2. The Legal Standard

In order to establish *prima facie* obviousness of a claimed invention, three criteria must be met. First, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981,180 USPQ 580 (CCPA 1974). Second, there must be some suggestion or motivation to combine the references. Third, there must be a reasonable expectation of success. Also, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art. *In re Vaeck*, 947 F.2d. 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In order for a claimed invention to be obvious, the invention as a whole must be considered, and in particular every limitation of the claim must be disclosed or suggested by the prior art. This means that for the present claims 1-6, the cited publications must disclose or suggest a method of transplanting hematopoietic cells from a donor source into a genetically unrelated recipient comprising administering to the recipient, in combination with the administration of the hematopoietic cells, an amount of mononuclear cells which are treated so as to substantially reduce their ability to cause graft versus host disease while they retain their ability to proliferate in the recipient and facilitate engraftment of the hematopoietic cells in the recipient; and administering to the recipient an effective amount of hematopoietic cells. For present claims 15-20, the cited publications must disclose or suggest a method of enhancing immune reconstitution in a transplant recipient, comprising administering to the recipient, in combination with a transplant, an amount of mononuclear cells which are treated so as to substantially reduce their ability to cause graft versus host disease while they retain their ability to proliferate in the recipient, and which are effective in enhancing immune reconstitution in the recipient. Appellants submit that the cited publications do not disclose or suggest all of these features.

Additionally, it has been established that the proposed modification or cannot change the principle of operation of the cited reference. That is, if a modification changes the principal operation of the prior art being modified, then the teachings are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). This means that the modification of Waller through the combination of Sykes must not change the principal operation of Waller which is the administration to the recipient, in combination with the administration of the hematopoietic cells, "an amount of mononuclear cells which are treated so as to render them incapable of proliferating and causing lethal graft versus host disease effect, but which are effective in enhancing subsequent engraftment of the hematopoietic cells in the recipient." Appellants submit that the modification of Waller proposed in the rejection would require an impermissible change in the principle of operation of Waller's method.

3. The Claims on Appeal

It has been recognized that T cells have both positive and negative effects when present in bone marrow transplant material. On the one hand, T cells are important for efficient engraftment of bone marrow cells in antigenically and genetically mismatched recipients. On the other hand, the presence of T cells in bone marrow transplants increases the incidence of graft versus host disease. In dealing with these effects, those performing bone marrow transplants have tried to balance removal and/or killing of T cells in bone marrow transplant material with retention of T cells in bone marrow transplant materials (Sykes is an example of this). Thus, the art recognized the presence or absence of T cells as being of significance to bone marrow transplants.

Appellants have discovered that it is not the mere presence or absence of T cells that matters in causing the positive and negative effects of T cells on bone marrow transplants. Specifically, Appellants have discovered that a reduction in the viability of T cells without eliminating or killing the T cells outright (that is, treating the T cells such that they retain their ability to proliferate) results in both the reduction of the negative effects of T cells on bone marrow transplants while retaining the positive effects. The present claims specifically claim treatment of mononuclear cells to obtain these benefits. Appellants submit that the cited publications do not disclose or suggest the claimed effects, do not disclose or suggest any way to obtain the claimed effects, and thus cannot make the present claims obvious.

The present claims are drawn to a method of transplanting hematopoietic cells from a donor source into a genetically unrelated recipient. To enhance the engraftment of the hematopoietic cells, mononuclear cells are administered with the transplanted hematopoietic cells. However, it has been recognized in the art that mononuclear cells also contribute to Graft versus Host Disease (GvHD). The claims overcome this problem by treating the mononuclear cells with an agent that reduces their ability to cause GvHD while maintaining their ability to proliferate. In particular, claims 1 and 15 recite that the mononuclear cells are "treated so as to substantially reduce their ability cause graft versus host disease while they retain their ability to proliferate in the recipient" (emphasis added). A careful reading of the claim language shows that the claims indicate that:

(A) the mononuclear cells are administered with the transplant (i.e., the hematopoietic cells from a donor source) and

(B) the mononuclear cells are "treated so as to substantially reduce their ability cause graft versus host disease while they retain their ability to proliferate in the recipient."

Note that property (A) requires that the cells be treated prior to administration to the recipient of the transplant. This property is crucial since treating donor mononuclear cells after they have been administered to the recipient would affect all of the mononuclear cells in the recipient, both donor and host mononuclear cells, and could leave the patient further immunocompromised. By treating only those mononuclear cells to be administered with the hematopoietic cell transplant, only those cells that could cause versus host disease are affected.

4. Waller (U.S. Patent No. 5,800,539)

Waller discloses the administration to the recipient, in combination with the administration of the hematopoietic cells, an amount of mononuclear cells which are treated so as to render them incapable of proliferating and causing lethal graft versus host disease effect, but which are effective in enhancing subsequent engraftment of the hematopoietic cells in the recipient (see, for example, the abstract; column 3, lines 5-16; column 4, lines 40-41; column 4, line 66- column 5, line1; and claim 1). Note that Waller specifically discloses that the mononuclear cells should not proliferate. This is exactly the opposite of the claimed method. Not only does Waller fail to disclose proliferation of donor mononuclear cells, Waller specifically teaches away from proliferation of donor mononuclear cells. Thus, because Waller

specifically discloses that proliferation should not occur, one of skill in the art would not be motivated to modify the method of Waller to require the proliferation of the mononuclear cells, as doing so would change the principle of operation of Waller.

5. Sykes et al. (WO 99/25367)

Sykes disclose the myeloreductive non-myeloablative treatment of mononuclear cells in the transplant recipient to reduce graft versus host disease. Note that Sykes treats the recipient mononuclear population not an *ex vivo* mononuclear population, and the treatment is in the recipient, not ex vivo as required by the claims on appeal (see, for example, page 2, lines 6-11; page 2, lines 18-26; and page 3, lines 1-12). Thus, for at least these reasons, Sykes fails to supplement the failings of Waller. Further, Sykes describes treatments that do not completely deplete the T cells present. Sykes does not disclose or suggest that the cells have **retained the ability to proliferate**. Sykes is silent on the proliferative ability of the remaining T cells. Thus, contrary to assertions in the rejection, Sykes does not disclose or suggest that the T cells retain the ability to proliferate.

Even if Sykes did encompass the use of treated donor T cells that retained the ability to proliferate (it does not), that would not make the present rejection proper. In this regard, Appellants note that art that encompasses (among other possibilities) a particular feature, but which does not disclose that particular feature, does not put those of skill in the art in possession of that particular feature. For example, art disclosing an alloy comprising some nickel does not disclose or make obvious an alloy comprising enough nickel to give the alloy a particular hardness. Until it is discovered that such an effect is possible and that such an amount of nickel is desirable, this particular alloy is unknown and unobvious to those in the art. The situation here is analogous. It is the Appellants who discovered the importance of the claimed treatment and features. None of the cited publications disclose or suggest treatment to obtain the claimed effects.

6. Combination of Waller and Sykes

The failings of the present rejection can be simply summarized. The claims require *ex vivo* treatment of mononuclear cells (that is, treatment prior to their administration to a recipient) and require that the treated mononuclear cells retain the ability to proliferate. First, neither Waller nor Sykes disclose or suggest that administered mononuclear cells retain the ability to

proliferate. In fact, Waller specifically requires that the administered mononuclear cells lack the ability to proliferate. Thus, neither of the cited publications disclose retention of the ability to proliferate. This alone is fatal to the rejection. Second, Sykes discloses treatment of the recipient patient, not *ex vivo* treatment of cells. Thus, the treatment disclosed by Sykes is not clearly relevant either to the claims on appeal or to Waller, and those of skill in the art would not be motivated to apply Sykes to the method of Waller. Finally, even if Sykes suggested *ex vivo* treatment of mononuclear cells such that they retain the ability to proliferate (it does not), this could not be applied to the method of Waller because to do so would result in the impermissible change in the principle of operation of the method of Waller (that is, such modification would require exactly the opposite state of proliferative ability than is required by Waller).

As discussed above, neither the Waller nor Sykes disclose or suggest the claimed invention. In fact in the Office Action mailed November 18, 2002, concedes that Waller does not disclose or suggest that the treated T cells retain their ability to proliferate in the recipient. The April 9, 2003 Office Action states that

> Sykes et al., teach a method of myeloreductive non-myeloablative treatment with fludarabine, the same type of treatment as [the] claimed invention. Sykes et al., teach that for successful transplantation of hematopoietic cells from donor to recipient, it is essential that after treatment T cells are not completely depleted, thus so called graft-versus-leukemia (GvL) effects of the non-depleted T cells help engraftment of donor hematopoietic cells (see page 10, lines 17-23, page 11, lines 5-25 in particular). Sykes et al., specifically stressed that said treatment should not completely eliminate T cells (page 16, lines 2-11 in particular).

Appellants respectfully point out that none of this establishes that Sykes discloses or suggests that the T cells retain the ability to proliferate nor that the T cells are to be treated ex vivo. Sykes is silent as to proliferation, and Waller requires non-proliferation. The rejection argues that because the claimed method results in mononuclear cells that retain the ability to proliferate, an allegedly similar treatment by Sykes must inherently result in T cells that retain the ability to proliferate. This reasoning is incorrect. First, Appellants' invention cannot be used to provide what is missing form the art (that is, retention of proliferative ability). Second, the

method of Sykes does not inherently result in the T cells that retain the ability to proliferate. In fact, in the absence of Appellants' invention, Waller indicates to those of ordinary skill in the art that a similar treatment (such as treatment with fludarabine) would result in cells that lack the ability to proliferate. It is not seen how the cited publications come close to providing the critical limitation of retention of the ability to proliferate required by the claims on appeal. Third, a merely possible, but undisclosed, property of a prior art composition does not meet the legal standard for inherency. An inherent property must necessarily be present in the prior art, not merely a possibility. Thus, even if the T cells of Sykes might possibly retain the ability to proliferate, that property cannot be inherent in the cells because it would not necessarily be present. Waller proves that retention of the ability to proliferate is not a necessary outcome of a treatment such as that of Sykes. For all of these reasons, the rationale of the rejection cannot be accepted. As a result, the present rejection fails and should be reversed.

Waller discloses a method of preventing graft-versus-host disease comprising treatment with fludarabine (see column 3, lines 6-16, which discuss the treatment, and column 4, line 66 through column 5, line 12, for the use of fludarabine, in particular). Waller also discloses that "lymphocytes, and especially T cells, present in the allogeneic bone marrow graft are important to ensure engraftment" (column 1, lines 52-55). Waller goes on to state that "T cells present in the allogeneic graft also have an important role in eliminating residual cancer cells in the recipient, a phenomenon termed "graft vs. leukemia effect" (column 1, lines 55-58). However, Waller is clear that the T cells are treated so as to render them **incapable** of proliferation (column 3, lines 6-16, column 5, lines 25-31, and claims 1 and 2).

Thus, both Waller and Sykes use fludarabine to reduce T cell populations. Further, only Waller discloses an effect of this use of fludarabine on the proliferative ability of the treated T cells (the proliferative ability is eliminated). In the face of this, it cannot be said that Sykes discloses (or is even consistent with the possibility) that the cells of Sykes retain the ability to proliferate. Accordingly, it would not be obvious to one of skill in the art to use fludarabine to result in T cells capable of proliferating.

Additionally, while Sykes does disclose that T cells should not be completely depleted, this is not the same as saying that the remaining cells would retain the ability to proliferate nor that such a characteristic would be desirable. The presence or absence of T cells in the recipient

is completely independent of their ability to proliferate. The art is replete with examples of non-proliferating T cells (see, for example, Jenkins MK, Schwartz, RH. (1987) *J. Exp Med.* 165:302-19; Jenkins MK, et al. (1987) *Proc Natl. Acad. Sci.* 84:5409-13; Quill H, Schwartz, RH. (1987) *J. Immnuol.* 138:3704-12). Appellants respectfully contend that the rejection extrapolates an effect that is not discussed anywhere in Sykes.

Furthermore, the rejection implies, in error, that any treatment with fludarabine would result in proliferating T cells--since that is what is presently claimed--and that Sykes intended that the T cells proliferate. This is incorrect. In fact, and to the contrary, Sykes discloses that "in preferred embodiments, immune cell activity, e.g., T cell activity, preferably graft reactive T cell activity, is inhibited in the subject" (page 14, lines 26-31). By this, Sykes means that the number of T cells is reduced. This is made clear where Sykes defines the term "immune cell activity" as "reducing the **number** of active immune cells, e.g., thymocytes, T cells...in a subject. Inhibition can include partial inhibition or partial reduction (as opposed to total elimination) of the number of active immune cells, e.g., T cells" (page 10, lines 18-22; emphasis added). This definition emphasizes reduction in the number of cells, not in any change in cell characteristics. Thus it is clear that Sykes viewed treatment with fludarabine as a means to reduce the T cell population not maintain the proliferative capacity of the T cells. This view of Sykes is further supported by embodiments that disclose "immunosuppression regimen for suppressing or depleting T cells in the transplanted donor stem cells" (page 5, lines 21-23, page 5, lines 31-33, page 21, lines 6-7, and page 21, lines 16-17), and by the statement (on page 2 lines 15-20) "[l]ikewise, the method can include the further step of treating the subject with an immunosuppressant regimen, after introduction of the donor stem cells.....[s]uch immunosuppressants can include independently of pre- and post-transplantation is [sic] both are carried out, a treatment of the subject which inactivates and/or depletes host T lymphocytes." If the goal, as indicated, is depletion, then surely the depleted cells cannot be expected to proliferate. Furthermore, it is clear throughout the specification and at least on page 15, lines 24-32, that in addition to donor derived T cells, host T cells are also to be depleted. Thus, it is clear that Sykes does not disclose or suggest the use of fludarabine to enable T cells to proliferate, but to the contrary discusses fludarabine only in the context of immunosuppression. For at least these reasons, the combination of Waller with Sykes does not make the claims obvious.

Moreover, it is clear that not all fludarabine treatments would result in a reduced T cell population that retains its proliferative capacity. The art is replete with examples of treatments with fludarabine that resulted in nonproliferative T cells. Waller is an example. Numerous publications in the area use fludarabine to eliminate T cells. Goodman et al., (1996) *Am. Surg.* 62(6):435-442, states that "[f]ludarabine phosphate selectively eliminates normal and malignant mononuclear cells in large animals and man." Additionally Goodman et al. report that "[t]he drug depletes mononuclear cells from culture within 24 hours of initial exposure, CD4 and CD8 T cells being more sensitive than either CD20 B cells or CD34 bone marrow precursors." Additionally, Boulad et al., (2000) *Br. J. Haematol.* 111(4):1153-7, discusses fludarabine-based cytoreductive treatment in a subject with Fanconi anaemia. Contemporary with Sykes and Waller, the art of hematopoietic stem cell transfers was filled with publications detailing the importance of reducing or depleting T cell populations to prevent graft versus host disease, not retaining T cells (see for example; Link, (1999) *Baillieres Best Pract Res Clin Haematol.* 12(1-2):87-98, and Slaper-Cortenbach, ICM, et al., (1999) *Rheumatology* 38:751-754). For at least these reasons, the combination of Waller with Sykes does not make claims obvious.

The rejection cites the paragraph on page 10, lines 17-23, of Sykes, which discusses the definition of "inhibiting immune cell activity," referring, in particular, to the last sentence which states "[i]nhibition can include partial inhibition or partial reduction (as opposed to total elimination) of the number of active immune cells e.g., T cells." The Examiner reads this to mean that total elimination is not desired (and thus, impliedly, that proliferation is desirable). However, the more reasonable reading of this passage is not that total elimination is undesirable, but rather a recognition that a small residual population of T cells would likely remain following treatment and therefore the Sykes specification was written to reflect that T cells may remain after treatment. This passage does not refer to the **proliferative** capacity of the T cells. As such, Appellants submit that this passage does not support the Examiner's position.

(9) SUMMARY AND CONCLUSION

Appellants have established that the claimed method is not obvious over Waller in view of Sykes. In particular, Appellants have established that (1) Waller and Sykes do not disclose or suggest a method of administering mononuclear cells treated so as to substantially reduce their

ability cause graft versus host disease while they retain their ability to proliferate in the recipient; (2) retention of proliferative ability is not inherent in the method of Sykes and thus is not present in the cited art, (3) the combination of Waller and Sykes would change the principle of operation of Waller and therefore cannot be used to establish a *prima facie* case of obviousness.

For the foregoing reasons, Appellants submit that the claims 1-6 and 15-20 are patentable and request reversal of the rejections.

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Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Robert A. Hodges
Reg. No. 41,074

NEEDLE & ROSENBERG, P.C.
Customer No. 23859
678/420-9300

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Robert A. Hodges

April 2, 2004
Date

APPENDIX 1: COPY OF CLAIMS INVOLVED IN APPEAL

1. A method of transplanting hematopoietic cells from a donor source into a genetically unrelated recipient, comprising:

a) administering to the recipient, in combination with the administration of the hematopoietic cells, an amount of mononuclear cells which are treated so as to substantially reduce their ability to cause graft versus host disease while they retain their ability to proliferate in the recipient and facilitate engraftment of the hematopoietic cells in the recipient; and

b) administering to the recipient an effective amount of hematopoietic cells.

2. The method of claim 1, wherein the mononuclear cells are T cells.

3. The method of claim 1, wherein the mononuclear cells are natural killer cells.

4. The method of claim 1, wherein the mononuclear cells are a mixture of T cells and natural killer cells.

5. The method of claim 1, wherein the cells are treated with a chemotherapeutic agent.

6. The method of claim 5, wherein the chemotherapeutic agent is selected from the group consisting of 9-D-arabinofuranosyl-2-fluoroadenosinemonophosphate (fludarabine), 2'-deoxcoformycin (pentostatin), 2-chlorodeoxyadenosine (2CDA), 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), 2'-deoxy-2', 2'-difluorocytidine (gemcitabine) and 2-amino-9-D-arabinosyl-6-methoxy-9-H-purine (Ara-G, 506U78).

15. A method of enhancing immune reconstitution in a transplant recipient, comprising administering to the recipient, in combination with a transplant, an amount of mononuclear cells which are treated so as to substantially reduce their ability to cause graft versus host disease while they retain their ability to proliferate in the recipient, and which are effective in enhancing immune reconstitution in the recipient.

16. The method of claim 15, wherein the mononuclear cells are T cells.

17. The method of claim 15, wherein the mononuclear cells are natural killer cells.

18. The method of claim 15, wherein the mononuclear cells are a mixture of T cells and natural killer cells.

19. The method of claim 15, wherein the cells are treated with a chemotherapeutic agent.

20. The method of claim 19, wherein the chemotherapeutic agent is selected from the group consisting of 9-D-arabinofuranosyl-2-fluoroadenosinemonophosphate (fludarabine), 2'-deoxcoformycin (pentostatin), 2-chlorodeoxyadenosine (2CDA), 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), 2'-deoxy-2', 2'-difluorocytidine (gemcitabine) and 2-amino-9-D-arabinosyl-6-methoxy-9-H-purine (Ara-G, 506U78).

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